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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,082	08/26/2003	Philip Dehayza	2055/100F558-US2	4920

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EXAMINER	
JONES, DWAYNE C	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,082	DEHAYZA ET AL.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/19/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-17 are pending.

2. Claims 1-17 are rejected.

Information Disclosure Statement

3. The information disclosure statement filed on February 19, 2004 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 6-13, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for functionalized hyaluronic acids with the crosslinker of a dihydrazide of the formula of claims 2 and 14, does not reasonably provide enablement for other types of derivatives of functionalized hyaluronic acids, including functionalized hyaluronic acids with other crosslinking agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

6. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to functionalized hyaluronic acids, including functionalized hyaluronic acids with other crosslinking agents, and other derivatives, as microspheres.

(2) The state of the prior art

The compounds of the inventions are hyaluronan as well as their functionalized derivatives; however, the prior art of Pouyani et al. of U.S. Patent No. 5,616,568 only teaches of a functionalized hyaluronate with dihydrazide.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art); In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the determination of the many different types of derivatives of hyaluronan prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to the plethora of compounds embraced by the phrase of "hyaluronan functionalized with a crosslinker at glucuronic acid sites" and are also referred to as "derivitized hyaluronan". The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.), cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires

more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of derivitized hyaluronan, in addition to making formulations with these derivatives of hyaluronan, there is insufficient enablement. The specification provides no guidance, in the way of enablement for other types of derivatives of hyaluronan other than those hyaluronan compounds that are crosslinked with a dihydrazide of the formula of claims 2 and 14. In addition, the specification does not provide any enablement of derivatives or analogues of hyaluronan that could be employed in this invention other than those derivatives of hyaluronan that are crosslinked with a dihydrazide of the formula of claims 2 and 14. The specification provides no guidance, in the way written description for derivatives of hyaluronan. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the

Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses derivatives of hyaluronan other than those hyaluronan compounds that are crosslinked with a dihydrazide. However, the instant specification only has enablement for hyaluronan other than those hyaluronan compounds that are crosslinked with a dihydrazide of the formula of claims 2 and 14, rather than all types of analogs that are embraced by the phrase, "derivitized hyaluronan".

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218

(CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the hyaluronan other than those hyaluronan compounds that are crosslinked with a dihydrazide of the formula of claims 2 and 14 that would be enabled in this specification.

7. Claims 1, 6-10, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. *Regents of the University of California v. Eli Lilly & Co.., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S.Ct. 1548 (1980),* holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly, 119 F.3d at 1566.* The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001),* which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, inter alia, "functional characteristics when coupled with a known or disclosed correlation between function and structure...." *Enzo Biochem, Inc. v. Gen-Probe., 296 F.3d, 316,*

1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp.2d 216, 225 (W.D.N.Y 2003).*

9. There is insufficient descriptive support for the phrase "hyaluronan functionalized", "functionalized hyaluronic acid" or even "derivitized hyaluronan" and the dihydrazide crosslinkers of the formula of claims 2 and 14. In addition, the instant specification does not describe what is meant phrase "hyaluronan functionalized", "functionalized hyaluronic acid" or even "derivitized hyaluronan" and the dihydrazide crosslinkers of the formula of claims 2 and 14. Structural identifying characteristics of the phrase "hyaluronan functionalized", "functionalized hyaluronic acid" or even "derivitized hyaluronan" and the dihydrazide crosslinkers of the formula of claims 2 and 14. There is no evidence that there is any per se structure/function relationship between the phrase "hyaluronan functionalized", "functionalized hyaluronic acid" or even "derivitized hyaluronan" and the dihydrazide crosslinkers of the formula of claims 2 and 14. The instant specification does provide an adequate written description for the phrase "hyaluronan functionalized", "functionalized hyaluronic acid" or even "derivitized hyaluronan", and the dihydrazide crosslinkers of the formula of claims 2 and 14. Accordingly, these claims fail to comply with the written description requirement.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 1, 4, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 1 recites the limitation "the derivitized hyaluronan" in line 2. There is insufficient antecedent basis for this limitation in the claim.

13. Claim 4 recites the limitation "the carboxyl groups" in line 1. There is insufficient antecedent basis for this limitation in the claim.

14. Claim 15 recites the limitation "The method of claim 8, wherein A is" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Illum of U.S. Patent No. 5,690,954. Illum is directed to using microspheres as drug delivery system to carry drugs, (see column 4, lines 6-13). In addition, Illum specifically

teaches that the use of microspheres greatly enhances the bioavailability of polar drugs, (see from column 8, line 43 to column 9, line 52). Illum teaches of the microspheres, which have bioadhesive properties, (see column 5, lines 14-22). Illum also teaches that the microspheres should be prepared form a biocompatible material such as hyaluronic acid, (see column 6, lines 13-19). Moreover, Illum teaches that the microspheres can be cross-linked, (see column 6, lines 22-26).

17. Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kyyronen et al. Kyyronen et al. teach of derivative microspheres of hyaluronic acid that are used to deliver a pharmaceutical, namely hydrocortisone, (see column 1, page 162).

18. Claim 6 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Illum of U.S. Patent No. 5,690,954. The is claims is defined as a product-by-process claim and is a product, not a process, see *In re Bridgeford*, 357 F2d 679, 149 USPQ 5 (CCPA 1966). It is the patentability of the product claimed and not of the recited steps which must be established, see In re Brown, 459 F2d 531, 173 USPQ 85 (CCPA 1972); *In re Wertheim*, 541 F2d, 191 USPQ (CCPA 1976). Accordingly, Illum is directed to using microspheres as drug delivery system to carry drugs, (see column 4, lines 6-13). In addition, Illum specifically teaches that the use of microspheres greatly enhances the bioavailability of polar drugs, (see from column 8, line 43 to column 9, line 52). Illum teaches of the microspheres, which have bioadhesive properties, (see column 5, lines 14-22). Illum also teaches that the microspheres should be prepared form a

biocompatible material such as hyaluronic acid, (see column 6, lines 13-19). Moreover, Illum teaches that the microspheres can be cross-linked, (see column 6, lines 22-26).

19. Claim 6 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kyyronen et al. Kyyronen et al. teach of derivative microspheres of hyaluronic acid that are used to deliver a pharmaceutical, namely hydrocortisone, (see column 1, page 162). The is claims is defined as a product-by-process claim and is a product, not a process, see *In re Bridgeford*, 357 F2d 679, 149 USPQ 5 (CCPA 1966). A comparison of the recited process with the prior art processes does not serve to resolve the issue concerning the patentability of the product, see *In re Fessman*, 489 F2d 742, 180 USPQ 324 (CCPA 1974).

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouyani et al. of U.S. Patent No. 5,616,568 in view of Kyyronen et al. Pouyani et al. teach of functionalized derivatives of hyaluronate that are cross-linked and are used to therapeutically deliver biological compounds, such as anti-infectives, anti-proliferatives, anti-virals, (see column and column 13, lines 7-21 and 55-67). Pouyani et al. also teach of various ways these functionalized derivatives of hyaluronate may be administered, (see from column 14, line 35 to column 15, line 20). It is also noted that Pouyani et al. further teach that the hyaluronic acid gels may be used for cosmetic purposes, (see column 15, lines 48-50). Moreover, Pouyani et al. disclose of a process to functionalized the hyaluronate by reacting hyaluronate with a dihydrazide while in the presence of carbodiimide, (see Scheme 1, column 4, lines 30-41). Pouyani et al. do not specifically teach of microspheres of hyaluronic acid; however, Pouyani et al. do state that functionalized hyaluronic acid compositions can be thought of as being composed of hydrophilic monomer units linked to form a soluble polymeric network and eventually crosslinked to form an insoluble network and that functionalized hyaluronic acid possesses a number of characteristics that make it advantageously used as a carrier of drugs, (see column 3, lines 44-51 and lines 60-65). The prior art reference of Kyyronen et al. teach of derivative microspheres of hyaluronic acid that are used to deliver a pharmaceutical, namely hydrocortisone, (see column 1, page 162). The determination of a dosage or a mode of administration having the optimum therapeutic index is well within the level of one having ordinary skill in the art, and the artisan would most

certainly be motivated to determine optimum amounts and modes of administration in order to get the maximum effect of the drug while in the functionalized derivatives of hyaluronate. Accordingly, the references make obvious the instant invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584. The official fax No. for correspondence is (703) 872-9306.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

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DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
May 31, 2004